

Book review:

MITOCHONDRIA by Immo E. Scheffler

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Reviewed by **Aubrey D.N.J. de Grey**

Rather a lot is known about mitochondria. As Scheffler notes in his Preface, the idea that one individual — however knowledgeable and experienced, and Scheffler is indisputably both of those — could compose a monograph on the entire topic of mitochondria is one that can reasonably inspire incredulity. Undaunted by this reaction, Scheffler took on the challenge; the result is not perfect, but it is certainly very valuable, and I doubt that anyone could have done better.

The possible role of mitochondrial dysfunction as a driving force in aging, so familiar to readers of this Journal, is mentioned gratifyingly early in the book — on the first page of the Preface, in fact. It is thus slightly disappointing to find that only five pages of the book are devoted to that topic. This should not be overstated, though: it is only by an in-depth understanding of mitochondrial function (such as is so ably presented throughout the rest of the book) that one can reason and speculate profitably about mitochondrial dysfunction, so in reality the mitochondrial gerontologist is much better served by the book as a whole than this statistic indicates.

A particular strength of the book is its historical coverage. Chapter 1 is devoted specifically to the history of mitochondriology from 1850 to 1988, but that brief summary (six pages) is supplemented throughout the book with liberal references to the pioneers who developed pivotal ideas and the controversies that drove the field. I found it a trifle irritating that researchers are generally referred to by their first initial and surname, rather than giving their first name in full; on reflection I realised that this convention annoyed me only because I was drawn so effectively into the history being described.

After a short (perhaps too short) chapter on the evolutionary origins of mitochondria, there is a detailed account of mitochondrial structure at the electron microscope level. Extensive space is deservedly given to illustrations of the extremely diverse morphology of mitochondrial cristae (the invaginations which allow the inner membrane surface area to exceed so greatly that of the outer membrane). Mitochondrial fusion is also discussed, as a lead-in to mitochondrial fission and turnover.

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For the next chapter we are regaled with a 93-page treatise on mitochondrial biogenesis, beginning with a survey of mitochondrial DNA content across the eukaryotes and moving through its replication and transcription, the synthesis of some proteins within the matrix and the import of others from the cytosol, and concluding with the much less understood processes of RNA import from the cytosol and regulated protein turnover within the matrix. Like the previous chapter, it rightly ends with a brief survey of the major unsolved problems that face workers in this field. Possibly the most challenging, and one with potentially great biomedical relevance, is the question of how the fabulously complex multisubunit enzymes of the respiratory chain are assembled.

The next two chapters focus on mitochondrial function. The treatment of electron transport and oxidative phosphorylation is extremely thorough and includes careful descriptions of the structures of the various enzyme complexes (to the extent they are known) as well as the variations on our OXPHOS machinery that are found in other eukaryotes. The chapter on other mitochondrial metabolic processes is surprisingly short, given that it ranges over not only the areas well known to undergraduate biologists (the Krebs cycle, beta-oxidation of fatty acids, the urea cycle) but also more esoteric and incompletely understood processes such as synthesis of coenzyme Q. Nevertheless, nothing essential is omitted from these sections.

The last long chapter (after which there is a brief discussion of mtDNA polymorphisms and their applications in the study of primate evolution and forensics) concerns the topic of most direct interest to readers of this Journal: mitochondrial dysfunction. This is Scheffler's own field — he was the first to isolate a respiration-deficient mutation in a mammalian cell culture. He has chosen to focus most of the chapter, however, on mutations in the mitochondrially-encoded components of the respiratory apparatus, which is not the focus of his own work. There is a good survey of mitochondrial diseases, followed by a rather brief discussion of the possibility that mtDNA mutations may underlie normal aging (focusing unduly, it seems to me, on a single and not enormously important study (1)), and then a summary of the still very speculative links between mtDNA mutations and various late-onset neurodegenerative diseases. A detailed treatment of the role of mitochondria in apoptosis also appears in this chapter; though that is an inappropriate location (given that apoptosis is usually a physiologically beneficial process, not a disease or a symptom of mitochondrial dysfunction), the coverage is thorough and accurate.

Inevitably there are areas of mitochondrial biology that Scheffler does not know in intimate detail, leading to

errors. In the areas which I know best I found important (albeit few) errors arising from ignorance of not particularly recent literature. For example, Scheffler states (p. 300) that the mosaic loss of cytochrome c oxidase activity in muscle has not been directly related to mtDNA mutations, something that Müller-Höcker in fact showed incontrovertibly in 1993 (2). Similarly, the generalisation (p. 178) that all three core subunits of cytochrome c oxidase are encoded in the mtDNA of all species was overturned in 1990 (3). Cytochrome c oxidase makes absolutely no superoxide (4), the hydroperoxyl radical is extremely reactive (5), an extracellular form of superoxide dismutase exists (6) and Down syndrome does not result from triploidy for cytosolic superoxide dismutase (7), all contrary to what is said or implied on pp. 235-237. Perhaps worst of all for readers of this Journal is the assertion (p. 298) that the mitochondrial DNA theory of aging is "a relatively novel concept", when in fact Harman famously wrote in 1972 (8) that:

"Free radicals 'escaping' from the respiratory chain ... would be expected to produce deleterious effects mainly in the mitochondria ... Are these effects mediated in part through alteration of mitochondrial DNA functions?"

But overall, the rarity of such oversights is extremely impressive. I therefore recommend this book to anyone who appreciates that, in order to understand how mitochondria may age us, one must first understand a great deal about how they sustain us for as long as they do.

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